REMARKS

A Request for Continued Examination is filed concurrently with this response. Claims 1, 2, 5, 8-11, 17, 25-27, 36, 37, 39, 50, 51 and 53 are pending in the application.

Claims 1, 2, 5, 8, 9-11, 17, 25, 26, 39, 50, 51 and 53 have been amended, and claims 77 and 78 have been added. Accordingly, claims 1, 2, 5, 8-11, 17, 25-27, 36, 37, 39, 50, 51, 53 , 77 and 78 will be pending in the application.

Claims 1, 2, 5, 8, 26 and 39 have been amended to track more closely corresponding method claims that were allowed in parent application Ser. No. 08/582,333 and issued in U.S. Patent 6,225,059, and/or to make minor editorial changes. Support for the claim amendments can be found throughout the specification and claims as originally filed and at least, for example, at page 27, line 21; at page 18, lines 14-16; and at page 66, line 4. Claims 9-11, 17, 25, 50, 51 and 53 have been amended to make formal changes. Claims 77 and 78 were added to claim more fully the invention. Support for the addition of claims 77 and 78 can be found throughout the specification and claims as originally filed and at least, for example, in original claims 28 and 29. No new matter has been added.

Amendment of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections in this or any previous office action, and was done solely to correct informalities and to more particularly point out and distinctly claim the subject matter that Applicants believe to be their invention in order to expedite prosecution. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Supplemental Information Disclosure Statement

Applicants file concurrently herewith a Supplemental Information Disclosure Statement ("SIDS") for the Examiner's consideration. Applicants are in the process of obtaining copies of the references cited in the SIDS and will forward same to the Examiner as soon as possible.

Rejection of Claims Under 35 U.S.C. § 101

Claims 1, 2, 5, 8-11, 17, 25-27, 36, 37, 39, 50, 51 and 53 are rejected under 35 U.S.C. § 101 as not supported by either a specific and substantial asserted utility or a well established utility. Applicants respectfully traverse the rejection for the reasons of record set forth in the response filed January 2, 2004 and for the further reasons discussed in detail below.

Claims 1, 2, 5, 8-11, 17, 25-27, 36, 37, 39, 50, 51 and 53 are directed to recombinant recombinant yeast cells comprising a recombinant gene encoding a heterologous orphan G protein-coupled receptor wherein the receptor is expressed on the cell membrane of the cell such that signal transduction activity is modulated by interaction with an extracellular signal; and a recombinant gene encoding a heterologous test polypeptide, wherein the test polypeptide is transported to a location allowing interaction with the receptor expressed on the cell membrane. The yeast cells are "autocrine" in that they are engineered to express the polypeptides to be tested for the ability ability to modulate the orphan G protein-coupled receptors expressed by the yeast cells. A collection of such yeast cells can be used to express a library of test polypeptides. The claimed recombinant yeast cells are used in screening assays to identify compounds, *e.g.*, ligands, that modulate the orphan G protein-coupled receptors expressed by the yeast cells.

The Examiner has rejected the claims as not supported by either a specific and substantial asserted utility or a well-established utililty, citing the reasons given in the previous office action (Paper No. 20 dated May 27, 2003). In the previous office action, the Examiner states that "a specific and substantial utility is one that is ***particular to the claimed subject matter and that identifies a 'real world' context for the claimed invention*** which does not require further research." (Paper No. 20, page 8, middle paragraph; emphasis added.) In the last paragraph on page 8 briding page 9 of Paper No. 20, the Examiner continues:

> "Since an orphan cell surface receptor has no known ligand and is not necessarily linked to any known biological functions, any known diseases or medical conditions, there is no specific and substantial utility for an orphan cell surface receptor. In addition, neither the specfication as filed nor art of record discloses or provides any evidence that points to a property of an orphan cell surface receptor such that another non-asserted utility would be well established. Thus, there is no well established utility for a mixture of recombinant yeast cells comprising the orphan cell surface receptor."

In the instant Office Action, the rejection is maintained for the reasons of record and is further predicated the Examiner's determination that although the claimed recombinant cells comprising orphan cell surface receptors can be useful tools for identification of receptor function, "such a research use is not a substantial utility." In addition, use of the cells to produce information relating to receptor ligands is stated to be "a research use and is not a substantial utility." The Examiner cites *Brenner v. Manson*, 383 U.S. 519 (1966) to support the rejection, alleging that in the Brenner case, a research utility was not considered a "substantial utility".

Applicants submit that clarifying the proper legal standard to be applied in assessing whether or not an invention lacks utility under 35 U.S.C. § 101 would be helpful in furthering prosecution of the instant application. *Brenner v. Manson*, 383 U.S.

519 (1966) held that a novel chemical process lacked utility where the resulting product was not known to have any biological activity. The Court in *Brenner* did not state, or even imply, that inventions for use in a research setting have no utility. Rather, it placed a bar on patentability where the sole purpose of an invention was to ascertain its importance. There is no authority which stands for the proposition that any and all research tools lack utility under § 101. Reliance on *Brenner v. Manson* (or any other case law) in this regard is misplaced.

The M.P.E.P. cautions that labeling an invention as a "research tool" is not reason enough to bring a rejection under 35 U.S.C. § 101. Specifically, M.P.E.P. §2107.01 provides as follows:

> Research Tools. Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, ***screening assays***, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). ***An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense.*** Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. ***Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention***. (Emphasis added.)

Such rejections are reserved for inventions "whose asserted utility requires further research to identify or reasonably confirm." Like the Court in *Brenner*, the M.P.E.P. only advocates rejection of inventions for which a utility is, at best, yet to be determined.

Recombinant cells of the present invention have a known utility that is specific and substantial. Orphan receptors expressed by recombinant cells of the invention have a

signal transduction activity that is triggered upon the binding of extracellular ligands. Thus, the cells are useful in ***screening assays*** to identify compounds, *e.g.*, ligands that modulate signal transduction activity through orphan G protein-coupled receptors. The Examiner should note that screening assays are one of the categories of inventions that M.P.E.P. §2107.01 specifically lists as having "a clear, specific and ***unquestionable*** utility (*e.g.*, they are useful in analyzing compounds)." (Emphasis added.)

The Examiner bases the rejection on the position that an orphan cell surface receptor has no known ligand and is not necessarily linked to any known biological functions, any known diseases or medical conditions and, therefore, has no specific and substantial utility. The Examiner's position assumes that the utility of the claimed yeast cells lies in the inate, though unknown, biological function of the orphan receptors as that relates to diseases and/or medical conditions.

That is not the case. The claimed yeast cells are useful regardless of the ultimate biological function of the orphan receptors they harbor. The goal of the invention is not to discern the biological function of the orphan receptor. The goal is to identify a ligand that modulates the signal transcution activity of the orphan receptor. Once that is done, the goal of the invention has been achieved. There is no invitation to do further research or need to do further research "to identify or reasonably confirm" the utility.

The utility of the claimed yeast cells lies in their ability to screen for and identify ligands that modulate the surrogate yeast signal transduction activity of the orphan receptors. The singular result of identifying such ligands is in and of itself useful in that it is a most important step in identifying the inate biological function of the orphan receptor.

Ligands identified by the screening assays of the invention using the claimed recombinant yeast cells comprise a class of compounds capable of binding to and modulating receptors that have a particular pharmacological activity (*i.e.*, signal

transduction activity). Although the receptors are orphan receptors, they nevertheless have signal transduction activity. In the pharmaceutical arts, it has long been held that practical utility may be shown by adequate evidence of any pharmacological activity. *Fugiwaka v. Wattansin*, 93 F.3d 1559, 1564 (Fed. Cir. 1996).[1] In producing and/or modulating signal transduction cascades, the cells and receptors of the invention all have a recognized pharmacological activity. It is this pharmacological activity, *i.e.*, signal transduction activity, the confers the ability to identify ligands that modulate the orphan receptors.

Cells of the invention produce a pharmacological activity that is both measurable and meaningful. Indeed, the recombinant cells of the invention derive their utility not only from their ability to generate this activity, but also from their use in identifying ligands that modulate the activity. Therefore, the claimed recombinant yeast cells are specifically and substantially useful under § 101 for the identification of ligands that modulate the activity.

As Applicants noted in their previous response, orphan receptors have been conserved in evolution and thus may be found throught the human body. Therefore, orphan receptors are clearly involved in important human biological functions. The claimed recombinant yeast cells that provide for the identification of ligands the bind to known orphan receptors have a specific and substantial utility because such ligand identification makes it is possible to (1) determine the function of the orphan receptor and (2) use the orphan receptor as a target for the discovery of new drugs. However, it is not possible to exploit these two opportunities without first identifying the ligands that

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[1] A novel class of compounds with activity similar to known pharmaceuticals (Nelson v. Bowler, 626 F.2d 853 (C.C.P.A. 1980)) or a demonstrated pharmacologic activity in vitro (Cross v. Iizuka, 753 F.2d 1040 (Fed. Cir. 1985)) have utility.

modulate the orphan receptors. The claimed invention provides this identifiable benefit and this alone is enough to establish a specific and substantial utility.

Indeed, the Court of Appeals for the Federal Circuit has held that an invention that confers some identifiable benefit, even one that is much less significant than that conferred by the instant ivention, meets the utility requirement under 35 U.S.C. §101. *See, Juicy Whip Inc. v. Orange Bang, Inc.*, 185 F.3d 1364, 51 USPQ2d 1700 (Fed. Cir. 1999). In elucidating the requirements imposed by 35 U.S.C. §101, the Federal Circuit held:

> "The threshold of utility is ***not*** high: An invention is 'useful' under Section 101 if it is capable of of providing ***some*** identifiable benefit. *See Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977F.2d 155, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ('To violate §101 the claimed device must be totally incapable of a useful result'); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) ('test for utility is whether invention is 'capable of ***any beneficial end***')". *Juicy Whip*, 185 F.3d at 1366; 51 USPQ2d at 1702. (Citations in original; emphasis added.)

The identification of a ligand of an orphan receptor is certainly "some identifiable benefit", is more than "any beneficial end", and is more than a useful result. As such, the claimed yeast cells that make this benefit possible meet the threshold of utililty.

The following section of the M.P.E.P. provides further guidance on the subject:

> **2107 Guidelines for Examination of Applications**
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> An invention has a well established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.... If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill

> in the art, do not impose a rejection based on lack of utility."
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> ***A rejection based on lack of utility should not be maintained if an asserted utility for the claimed invention would be considered specific, substantial, and credible by a person of ordinary skill in the art in view of all evidence of record.*** Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. Similarly, Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered. (emphasis added).

Applicants submit that those of ordinary skill in the art who populate the pharmaceutical industry throughout the world have recognized the utility of the claimed invention based on the benefit of identifying ligands of orphan receptors. In the regard, Applicants invite the Examiner's attention to the documents attached hereto as Appendix A.

Page 82, excerpted from the PharmaVitae 2003 (Datamonitor) of Takeda Pharmaceutical Corporation ("Takeda"), shows that a major thrust of Takeda is to discover new drug targets by searching orphan receptors with unknown ligands and clarifying their physiological functions. Although Takeda is currently using a genomic data base, one of ordinary skill in the art will readily consider the instant invention as useful in clarifying the physiological functions of orphan receptors (by indentifying ligands that modulate the activity of the orphan receptors).

Likewise, Fujisawa Pharmaceutical Company Limited ("Fujisawa) is keenly interested in discovering chemical compounds that modulate orphan G protein-coupled receptors ("GPCRs"). Page 75 excerpted from the PharmaVitae 2000 (Datamonitor) of

Fujisawa describes an agreement between Fujusawa and Arena Pharmaceuticals, Inc. ("Arena"). Pursuant to the agreement, Arena will provide Fujisawa with screening assays developed using Arena's proprietary Constiutively Activating Receptor Technology ("CART") for the purpose of discovering chemical compounds acting upon selected orphan receptors whose function and natural ligand are unknown. Although the CART technology is somewhat different than the claimed invention, the goal of CART, and hence the utilty – identifying compounds, *e.g.*, ligands, that modulate the activity of an orphan receptor –, is the same as the claimed invention. Indeed, the claimed technology would most likely compete directly with CART.

Arena is a biopharmaceutical company that engages in the research and development of drugs that act upon GPCRs. As noted above, its CART technology provides screening assays that identify chemical compounds acting upon orphan receptors whose function and natural ligand are unknown. It has been extremely successful in licensing its CART technology to various pharmaceutical companies. This success is a testament to the utilty of CART and the similar screening assays made possible by use of the claimed yeast cells.

In this regard, Applicants invite the Examiner's attention to Appendix A and the "RECAP" allilance summaries of Arena agreements/collaborations (and associated press releases) with Fujisawa (CART validation of 13 orphan GPCRs), Merck (validating and developing therapeutics on three orphan GPCRs using CART) and Lily (CART activation of GPCRs). These licensing/collaboration activites are evidience of the utility of the claimed invention, a utility that has been widely recognized and seized upon by those of ordinary skill in the art.

In addition, numerous courts have held that proof of utility is further supported by evidence of commercial success. To paraphrase, these courts have held that if someone wants to buy/license the invention, then it has "real world" utilty. *See*, *e.g.*, *In re*

Peddrick, 48 F.2d 415, 418 (C.C.P.A. 1931); *McClain v. Ortmayer*, 141 U.S. 419, 430 (1931); *Boss Mfg. Co. v. Thomas*, 182 F. 811, 814 (8th Cir. 1910); *In re Husted*, 39 F.2d 713, 715 (C.C.P.A. 1930); *In re Holt*, 162 F.2d 472, 478 (C.C.P.A. 1947); *Technicon Instruments Corp. v. Alpkem Corp.*, 664 F.Supp. 1558, 1581 (D.Or. 1986); *Photon, Inc. v. Eltra Corp.*, 308 F.Supp. 133, 141 (N.D.Ill. 1969); *Panduit Corp. v. Stahlin Bros. Fibre Works, Inc.*, 298 F.Supp. 435, 442 (W.D.Mich. 1969); *Leach v. Rockwood & Co.*, 273 F.Supp. 779, 786 (W.D.Wis. 1967); *Continental Can Co. v. Anchor Hocking Glass Corp.*, 362 F.2d 123, 124 (7th Cir. 1966); *Spring-A-Way Displays of Cal., Inc. v. Ad-Rack, Inc.*, 249 F.Supp. 368, 369 (S.D.Ohio 1965); *University of Illinois Foundation v. Block Drug Co.*, 133 F.Supp. 580, 588 (E.D.Ill. 1955); *Carbide & Carbon Chemicals Corp. v. Coe*, 102 F.2d 236, 241 (C.A.D.C. 1938); *Baltimore Paper Co. v. Oles Envelope Co.*, 13 F.Supp. 951, 958 (D.Md. 1936). Applicants again invite the Examiner's attention to Appendix A and the "RECAP" allilance summaries and of Arena agreements/collaborations with Fujisara, Merck and Lily. The deals with Fujisara, Merck and Lily were worth $12 million, $41.2 million and $27.8 million, respectively. In view of the cited cases, this is certainly evidence of the utility of technology that enables the identification of compounds that modulate orphan receptors.

Therefore, in accord with with the M.P.E.P. and applicable case law, an asserted utility has been provided for the claimed invention that is specific, substantial, and credible, and would be considered as much by a person of ordinary skill in the art in view of all evidence of record. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claims 1, 2, 5, 8-11, 17, 25-27, 36, 37, 39, 50, 51 and 53 are rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. The Examiner alleges that because

the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention. Applicants respectfully traverse the rejection for the reasons of record and reiterate those reasons herein, and for the additional reasons detailed below.

In their response to the rejection of the claims under 35 U.S.C. §101, Applicants have established that the claimed invention is supported by a specific and substantial asserted utility or a well established utility. Further, Applicants have amended the claims to recite recombinant yeast cells comprising heterologous orphan G protein-coupled receptors. Applicants submit that these claims, when read in light of the specification, in particular working Examples 9 and 10 directed to identifying ligands of the orphan G protein-coupled receptors FPRL-1 and MDR-15, respectively, are fully enabled. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims Under 35 U.S.C. § 103

Claims 1, 2, 5, 8-11, 17, 25-27, 36, 39, 50 and 53 remain rejected under 35 U.S.C. § 103 as being unpatentable over King *et al.* (*Science* 250:121. 1990) in view of Devlin *et al.* (*Science* 249:404-406, 27 Jul. 1990), Scott et al. (*Science* 249:386-390, 27 Jul. 1990), and Cwirla et al. (*P.N.A.S.* 87:6378-6382, Aug. 1990) and Ladner *et al.* patent (U.S. Pat. Ser. No. 5,096,815) for the reasons set forth in the previous Office Action (Paper No. 20, May 27, 2003). Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness for the claimed invention, there must have been some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in the manner proposed by the Examiner. Second, there must have been a reasonable expectation of success at the time the

invention was made. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See M.P.E.P. 2143.

The Examiner relies on the King *et al.* publication as teaching the construction of a yeast cell of the species *Saccharomyces cerevisiae* which expresses a human beta2-adrenergic receptor, which is a heterologous G-protein-coupled receptor, a heterologous Gα subunit of a G protein which places the endogenous pheromone response pathway under the control of the heterologous receptor and a lacZ reporter gene under the control of the pheromone responsive FUS1 gene promoter. The Examiner continues that King *et al.* also teach that "the ability to control the yeast pheromone response pathway by expression of a heterologous adrenergic receptor and its cognate G protein α subunit may facilitate structural and functional characterization in yeast of mammalian G protein coupled receptors. By scoring for growth arrest or β-galactosidase induction, the functional properties of mutant receptors can now be rapidly tested' and 'as additional genes for putative G protein-coupled receptors are isolated, numerous ligands can be screened to identify those with activity toward previously unidentified receptors". The Examiner clearly admits that "King *et al.* fail to teach yeast cells that express a variegated population of receptor effector polypeptides to be tested endogenously".

The Examiner relies on each of Devlin *et al.*, Scott *et al.* and Cwirla *et al.* references as teaching construction of random peptide libraries on phage for screening to identify ligands, e.g., ligands for hormone receptors and enzymes.

The Examiner relies on Ladner *et al.* as teaching screening for DNA-binding proteins by variegation of genes encoding known binding proteins and selection for proteins binding the desired target DNA sequence. With regard to the requisite suggestion and reasonable expectation of success in making the claimed invention, the Examiner states:

> it would have been obvious to one having ordinary skill in the art as the time the invention was made to construct a library of random peptides as taught by Devlin *et al.*, Scott *et al.*, Cwirla *et al.* or Ladner *et al.* in the yeast cells taught by King *et al.* to produce a mixture of recombinant yeast cells containing an expressible recombinant gene encoding a heterologous cell surface receptor and an expressible recombinant gene encoding a heterologous potential receptor effector polypeptide with a reasonable expectation of success. One would have been motivated to do so because use of peptide libraries is useful and efficient in screening for peptide ligands as taught by Devlin *et al.*, Scott *et al.*, Cwirla *et al.* or Ladner *et al.*

Applicants respectfully disagree. There are a number of reasons why the claimed invention is not *prima facie* obvious in view of the cited references, in addition to the reasons made of record in Applicants response filed January 2, 2004. For reasons discussed in further detail below, the Examiner has failed to establish a prima facie case of obviousness because there was neither a suggestion in the prior art to combine the references in the manner proposed by the Examiner to arrive at the claimed invention, nor was there a reasonable expectation of success at the time the invention was made. Furthermore, the proposed combination of references neither teaches nor suggest each and every element of the invention as claimed.

I. Lack of Motivation/Suggestion

A. Combination of King and Devlin/Scott/Cwirla

The Examiner relies on the combination of King et al. and Devlin/Scott/Cwirla to provide the suggestion to use the King system, in which GPCR are expressed on yeast cells, to screen a library of random peptides to thereby identify receptor agonists or antagonists. However, at the time the invention was made, the ordinarily skilled artisan would not have been motivated to combine the teachings of King *et al.* and Devlin/Scott/Cwirla because of technical hurdles that would have made it impossible to use the random peptide libraries of Devlin/Scott/Cwirla in the system of King *et al.*

More specifically, Devlin/Scott/Cwirla teach random peptide libraries that are expressed as fusions to the coat protein on the surface of phage. Thus, these random peptides are chimeras of the phage coat protein, which serve as a support to allow for physical isolation of phage DNA expressing a selected peptide of interest, enabling recovery and characterization of the peptide.

The system of King *et al.* utilizes yeast cells that express a heterologous GPCR in their cell membrane. As is well known in the art, the cell membrane of yeast is surrounded by a cell wall. When considering King in combination with Devlin/Scott/Cwirla, it would have been readily apparent to the ordinarily skilled artisan that one could not utilize the random peptide libraries expressed on phage taught by Devlin/Scott/Cwirla in the system of King *et al.* because the phage expressing the peptides would be unable to cross the yeast cell wall and therefore would be unable to gain access to the heterologous GPCR expressed on the yeast cell membrane. Because the peptide libraries of Devlin/Scott/Cwirla could not interact with the GPCRs of King *et al.*, the ordinarily skilled artisan would not have been motivated to combine the teachings of these references.

B. Combination of King and Devlin/Scott/Cwirla and Ladner

The Examiner further relies upon Ladner *et al.* for the motivation to express the random peptide library within the yeast cell. However, for various reasons discussed below, the ordinarily skilled artisan would not have been motivated to combine the teachings of King and Devlin/Scott/Cwirla with Ladner *et al.*

First, Ladner *et al.* explicitly teaches away from the practice of using yeast cells as the host cell for intracellular library expression. For example, Ladner *et al.* state that ***"[b]acterial cells are preferred over yeasts***, fungi, plant, or animal cells ***because they are superior on every count"*** (see column 22, at line 32; emphasis added). Ladner *et al.*

further teach that because of the low efficiency of DNA uptake into yeast cells they are ***"not now preferred for the process described in this patent.*** . . . " (see column 24, at line 1; emphasis added). Although Ladner *et al.* state that the uses of "yeasts and mammalian systems are described further below" (see column 22, at line 39), Applicants have found no such teachings in the Ladner *et al.* reference disclosing how to successfully express peptide libraries in an "autocrine" fashion as in the yeast cells of the invention. At column 22, line 47, Ladner *et al.* merely make a prophetic statement that "because the intended use of novel DBPs [DNA Binding Proteins] will often be in eukaryotic cells, some final development and testing may be done in eukaryotic cells such as *Saccharomyces cerevisiae* or Chinese hamster ovary cells." Moreover, Ladner *et al.* do not describe or exemplify ***screening*** of a library in yeast cells. Furthermore, at column 85, line 14 under "Choice of Cell Line or Strain", Ladner *et al.* teaches only bacterial cells. If the Examiner contends that Ladner *et al.* has enabled the use of yeast cells, Applicants request that the Examiner specifically point out such teachings in the Ladner *et al.* patent.

Second, Ladner *et al.* pertains to the specific problem of designing and selecting novel DNA binding proteins and does not teach or suggest that the methods disclosed in that patent could be extended beyond the identification of DNA binding proteins, such as to be used in the identification of ligands for orphan GPCRs. As plainly taught by Ladner *et al.*, "[o]ur goal is the development, in part by conscious design and in part by in vivo selection, of a protein which binds to a DNA sequence of significance. . . ." (See column 32, at line 62). The Ladner *et al.* system uses a library of mutants of known DNA binding proteins that have "variegation" in their DNA binding domains. Thus, the libraries of Ladner *et al.* are not random peptide libraries but rather libraries of variants of DNA binding proteins. The Ladner *et al.* patent teachings are *all* based on mutating known

DNA binding proteins, such as Cro and phage p22 Arc, within their DNA binding domain.

II. Lack of Reasonable Expectation of Success

In addition to the foregoing, a *prima facie* case of obviousness has not been established because there was no reasonable expectation of success in making the claimed invention.

As discussed above, the pending claims pertain to methods of using recombinant cells, in which several different components are expressed by the cells and in which a variety of functional interactions are achieved. In particular, in the system of the invention of the claims presented herein, the heterologous orphan cell surface receptor is "expressed on the cell membrane of said cell such that signal transduction activity via said receptor is modulated by interaction with an extracellular signal." Additionally, the test polypeptide co-expressed in the cell is "transported to a location allowing interaction with the receptor expressed on the cell membrane." Still further, the mixture cells expresses a library of polypeptides wherein "modulation of the signal transduction activity of the orphan cell surface receptor by one of the heterologous test polypeptides within the library that reacts with said orphan cell surface receptor will provide a detectable signal."

At the time the invention was made, there simply was no reasonable expectation that each of these elements could be achieved to create successfully a system that detects a functional interaction between a heterologous orphan cell surface receptor expressed on a cell and a test polypeptide within a library that is expressed by the cell in an autocrine fashion. In fact, the teachings of the prior art provide several reasons that indicate that one of ordinary skill in the art, at the time the invention was made, would not have expected the claimed invention to be successful, as discussed further below.

The Ladner *et al.* reference, the only cited reference that pertains to intracellularly expressed libraries, provides no reasonable expectation of success that an intracellularly expressed polypeptide could achieve a ***functional*** interaction with a target binding protein. The DNA-DNA binding protein interactions taught by Ladner *et al.* all involve the ***direct binding*** of a protein to DNA. In the system taught by Ladner *et al.*, there is no requirement that the variegated portion of the proteins expressed in the library of Ladner *et al.* (*i.e.*, the mutated DNA binding domains) have any functional activity beyond binding to DNA. The ultimate ability of the library members to activate reporter gene expression resides in the transcriptional activation domain of the DNA binding protein, but this domain is not variegated. Thus, Ladner *et al.* teach methods of identifying DNA binding proteins of interest, which methods are all based on detecting a DNA ***binding*** interaction.

In contrast, the instant invention involves a ***functional interaction*** between an intracellularly expressed library polypeptide and a target orphan receptor. In accordance with the present invention, the library member not only interacts with, *e.g.*, bind to, the target orphan receptor, but also ***functionally*** interacts such that the receptor generates an intracellular signal that leads to a detectable signal. The ability to bind does not necessarily indicate the ability to functionally modulate. A showing that a polypeptide can bind to a target provides no reasonable expectation that the polypeptide can functionally modulate the target and thereby provide a detectable signal. Thus, Ladner *et al.* provides no reasonable expectation that the claimed invention, which involves a ***functional*** interaction between the test polypeptide and the orphan GPCR, could be successfully achieved.

Still further regarding the claim recitation that the test polypeptide be "transported to a location allowing interaction with the receptor expressed on the cell membrane", there was no reasonable expectation of success that this could be achieved for the system

of the invention. Although there were examples in the art of the use of a signal sequence to direct secretion of a heterologous polypeptide in a host cell, the ability of any particular signal sequence to direct secretion of any particular heterologous polypeptide is highly variable and unpredictable. There are a number of factors that could have led to failure to successfully transport the polypeptides to a location allowing interaction with the receptor expressed on the cell membrane. For example, fusion of a signal sequence could have altered the conformation of the signal sequence such that it no longer could mediate transport. Additionally or alternatively, fusion of a signal sequence could have altered the conformation of the potential orphan receptor ligands such that "true" ligands within the library could no longer functionally interact with the orphan receptor at the cell membrane. Still further, expression of the library of fusion polypeptides might have interfered with the normal workings of the transport pathway such that the library of polypeptides failed to reach a location that allowed for interaction with the orphan receptor. Accordingly, there was no reasonable expectation of success that test polypeptides could be successfully expressed in yeast such that they are "transported to a location allowing interaction with the receptor expressed on the cell membrane." GPCR expressed on the cell membrane of the yeast cells would provide a detectable signal.

Again, it must be emphasized that none of the five cited references is concerned with secretion of heterologous test polypeptides by yeast cells. In summary, there was no reasonable expectation of success in making the claimed recombinant cells that: 1) express a heterologous orphan GPCR "on the cell membrane of said cell such that signal transduction activity via said receptor is modulated by interaction with an extracellular signal"; 2) express a test polypeptide that "is transported to a location allowing interaction with the receptor expressed on the cell membrane"; and 3) collectively express a library of test polypeptides wherein "modulation of the signal transduction activity of the orphan

cell surface receptor by one of said heterologous test polypeptides [within the library] that reacts with said orphan cell surface receptor will provide a detectable signal." For reasons discussed above, lack of any one of these functions is sufficient to create a lack of reasonable expectation of success for the claimed invention. Accordingly, in view of the numerous potential pitfalls discussed herein, there is no way that one can conclude that there was a reasonable expectation of success in making the claimed invention in view of the teachings of the cited references.

II. The Cited Art Does Not Teach or Suggest All of the Claim Limitations

Even if the cited references were combined in the manner proposed by the Examiner, this combination simply does not result in the claimed invention. To establish a *prima facie* case of obviousness, all of the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974) (see also M.P.E.P. 2143.03). In the instant situation, the methods recite that "the test polypeptide is *transported to a location allowing interaction with the receptor expressed on the cell membrane*" (emphasis added). This claim limitation is not taught or suggested by any of the cited references, alone or in combination. The Ladner *et al.* patent, which is the only one of the five cited references which is relied upon for teaching or suggesting expression of a heterologous polypeptide *in* a host cell, only teaches or suggests expressing the polypeptide intracellularly, to allow for interaction with a DNA binding protein that also is expressed entirely intracellularly. Thus, even if one were to combine the five cited references as proposed, this would not result in a method in which a test polypeptide is *transported to a location allowing interaction with the receptor expressed on the cell membrane*.

Applicants note that the foregoing arguments were made in the parent application to traverse the same five references that were cited under 35 U.S.C. §103 and were

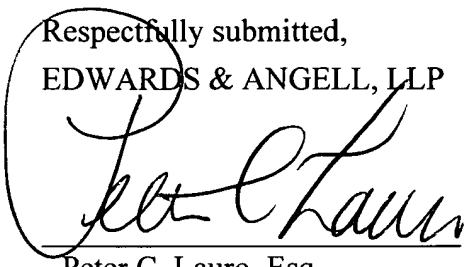
successful in obtaining allowance of corresponding method claims that issued as U.S. Patent 6,225,059. The instant composition claims are essentially the same as the method claims of the patent but for the recitation of "orphan".

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants respectfully request entry of the amendments reconsideration and withdrawal of all pending rejections, and allowance of this application with claims 1, 2, 5, 8-11, 17, 25-27, 36, 37, 39, 50, 51, 53, 77 and 78. If a telephone call or personal inteview with Applicants' attorney would be helpful in expediting prosecution of the application, the Examiner is invited to call the undersigned at the telephone number indicated below.

Respectfully submitted,
EDWARDS & ANGELL, LLP



Peter C. Lauro, Esq.
Registration No. 32,360
Attorney for Applicants

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Boston, MA 02205
(617)517-5509

Date: October 19, 2004

APPENDIX A

DATAMONITOR

PharmaVitae 2003

Takeda

Takeda faces declining sales due to a portfolio of mature products and a weak late stage pipeline

With a strong financial position Takeda must take action in order to secure continued growth, either through further in-licensing agreements or acquisitions

Reference Code: CSHC1084

Publication Date: 07/2003

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Using Celera's genomic database, Takeda has been conducting research aiming to discover new drug targets by searching orphan receptors with unknown ligands and clarifying their physiological functions. In addition, research has been carried out on disease-specific regulated genes. The information provided by GeneExpress will be beneficial in clarifying the gene functions and the value of the new targets, and in predicting toxicity at an earlier stage of research.

D A T A M O N I T O R

Market Analysis Experts

PharmaVitae 2000

Fujisawa Pharmaceutical Co., Ltd.

Reference Code:
CSHC0217

One Park Avenue	108-110 Charles House	Messe Turm	2802-2803 Admiralty
14th floor, New York	Finchley Road	Box 23	Centre, Tower 1
NY 10016-5802	London NW3 5JJ	60308 Frankfurt	18 Harcourt Road
USA	United Kingdom	Deutschland	Hong Kong
t: (+1) 212 686 7400	t: (+44) 020 7675 7000	t: (+49) 69 97 54 43 20	t: +(852) 252 90356
f: (+1) 212 686 2626	f: (+44) 020 7675 7500	f: (+49) 69 97 54 49 00	f: +(852) 252 90356
e: ussales @ datamonitor.com	e: uksales @ datamonitor.com	e: desales @ datamonitor.com	e: hksales @ datamonitor.com

w w w . d a t a m o n i t o r . c o m

compound using IGI's patented Novasome microencapsulation technology. Under the terms of this agreement, IGI will receive an upfront payment and will be eligible to receive milestone payments as product development proceeds.

Arena Pharmaceuticals

On 31 January 2000, Fujisawa announced that it had concluded a collaborative research agreement with Arena Pharmaceuticals, Inc. for the discovery of new drugs in the neurodegenerative disease area. Arena is a biotechnology company conducting research into new drugs utilizing its Constitutively Activating Receptor Technology (CART) which allows for efficient exploration of chemical compounds acting upon orphan receptors whose function and natural ligand are not known.

Under the agreement, Arena will provide Fujisawa with screening assays developed utilizing CART for the purpose of discovering chemical compounds to selected orphan G protein-coupled receptors. Fujisawa will also obtain worldwide and exclusive development, manufacturing and marketing rights on the resulting products. Though financial terms are not disclosed, Arena may receive milestone payments and royalty payments on sales of drugs discovered through the collaboration.

Transduction Laboratories

In July 1999, Fujisawa entered into an exclusive marketing agreement with Transduction Laboratories to market its cell biology reagents line in Japan. This agreement will help Fujisawa to expand its immunology reagents product line, given that the company already markets flow cytometry reagents.

Aventis

In July 1999, Fujisawa entered into an optional and license agreement with Aventis (formerly Hoechst Marion Roussel) for a series of malononitrilamide compounds (MNAs) with immunosuppressive activity. MNAs, discovered by Aventis, have a novel mechanism of action different from Fujisawa's immunosuppressant, Prograf, as they inhibit bio-synthesis of pyrimidine in both B-cell and T-cell.

Under the agreement, Fujisawa has the option to acquire the exclusive worldwide marketing rights to Aventis' MNAs. While the agreement focuses on transplantation, dermatological diseases and certain auto-immune diseases as its primary targeted indications, Fujisawa will initially develop MNAs for the transplantation field. Aventis will retain the rights to develop the compounds for the indication of cancer, rheumatology and central nervous system. Financial terms were, however, not disclosed.

The information presented here is a high-level summary of the agreement with basic information and key indexing terms. For some agreements, a Contract Analysis is available. For a sample Contract Analysis, click on the link.

This agreement is FILED. The contract is ANALYZED. Analysis Cost: US$200. Contracts Cost: US$200. Delivery: Immediate upon processing of order.

This agreement's Contract Analysis and full filed contract(s) may be read online by rDNA.com subscribers. For an explanation of the rDNA.com service, visit the information site.

R&D: Arena Pharmaceuticals
Client: Fujisawa
Parent: Astellas Pharma

Date: 01/2000
Parties: Drug / Biotech
Type: Development, License, Research, Option
Subject: CART validatation of 13 orphan GPCRs

Press Release(s):

$ Terms: Partial
Size ($M): $12.0
Equity ($M):
Royalty:

Disease:
Technology: Screening, Gene Expres
Stage At Signing: Lead Molecule

01/31/2000

View this Alliance Summary

Arena Pharmaceuticals and **Fujisawa**
CART validatation of 13 orphan GPCRs
Web Link: http://www.arenapharm.com/investor/inv.htm

Arena Pharmaceuticals Begins Receptor Drug Discovery Collaboration With Fujisawa

SAN DIEGO, Jan. 31, 2000 -- Arena Pharmaceuticals, Inc. ("Arena"), a privately held biopharmaceutical company, today announced that Arena and Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan ("Fujisawa") have entered into a collaboration involving Arena's proprietary CART(TM) Technology. Under the terms of the agreement, Arena and Fujisawa will jointly validate selected orphan G protein-coupled receptors (GPCRs) as drug screening targets. Arena will be responsible for receptor identification, localization and regulation, application of its CART Technology to Fujisawa-selected receptors, and validation of screening assays based upon such selected receptors. Fujisawa will be responsible for screening of its chemical compound library using selected CART receptor assays, identification of chemical leads, and pre-clinical and clinical development of such leads. The collaboration also includes the opportunity for screening of the selected receptors by Arena using Arena's in-house chemical library. Though details regarding financial terms are not disclosed, the agreement provides for Arena to receive assay license, milestone and royalty payments on sales of drug products discovered under the collaboration.

"We are very pleased to have established this interactive collaboration with Fujisawa," stated Jack Lief, President & CEO of Arena. Mr. Lief further noted that, "Fujisawa has extensively reviewed our CART Technology and believes that our joint efforts will beneficially enhance Fujisawa's new drug pipeline in the area of neurodegenerative diseases and disorders."

Founded in April of 1997, Arena is primarily focused on the discovery and development of novel therapeutic modulators of GPCRs, using its proprietary CART Technology. CART allows for the direct identification of such modulators at these receptors in a ligand-independent manner, making the technology particularly useful with respect to the over 2,000 orphan GPCRs that are estimated to be a part of the human genome.

Fujisawa Pharmaceutical Co., Ltd., headquartered in Japan, is a pharmaceutical company with a firm commitment to innovative research in its quest to satisfy unmet medical needs and contribute to the progress of medical care. Fujisawa is active in the world major pharmaceutical markets, Japan, North America, Europe and Asia, with sales outside Japan accounting for more than a third of net sales. Neurological diseases and disorders, in particular stroke, are among the major research areas for Fujisawa. Fujisawa expects that the collaborative relationship with Arena will complement Fujisawa's internal research efforts in the pursuit of new products in this area.

01/31/2000

View this Alliance Summary

Arena Pharmaceuticals and **Fujisawa**
CART validatation of 13 orphan GPCRs
Web Link: http://www.arenapharm.com/investor/inv.htm

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This agreement is FILED. The contract is UNANALYZED. Analysis Cost: US$300. Contracts Cost: US$200. Delivery: 3 to 5 business days

This agreement's full filed contract(s) may be read online by rDNA.com subscribers. For an explanation of the rDNA.com service, visit the information site.

SAMPLE ORDER VIEW C

R&D: Arena Pharmaceuticals
Client: Merck

Date: 10/2002
Parties: Drug / Biotech
Type: Development, License, Research
Subject: G protein-coupled receptor (GPCR) therapeutics

Press Release(s):

$ Terms: Partial
Size ($M): $41.2
Equity ($M):
Royalty:

Disease:
Technology: Combinatorial, Microarr
Stage At Signing: Discovery

10/16/2002

View this Alliance Summary

☐

Arena Pharmaceuticals and **Merck**

G protein-coupled receptor (GPCR) therapeutics

Web Link: http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=ARNA&script=410&layout=-6&item_id=345523

☐

Arena Pharmaceuticals, Inc. Announces Multi-Year Drug Discovery Collaboration With Merck & Co., Inc.

SAN DIEGO, Oct 16, 2002 /-- Arena Pharmaceuticals, Inc. (Nasdaq: ARNA) (Arena) announced today that it has entered into a multi-year research and licensing agreement with Merck & Co., Inc. (Merck) to collaborate on validating and developing therapeutics on three orphan G protein-coupled receptors (GPCRs) of particular interest to Merck. Arena will utilize its proprietary receptor technologies, CART and Melanophore, as well as the efforts of its medicinal chemistry group, to discover and develop initial molecules on these GPCRs. These efforts are expected to be supplemented by the efforts of chemists and other scientists at Merck. The objective of the research and development effort is to discover and commercialize novel compounds with therapeutic potential on these GPCRs.

Under the collaboration, Arena will receive an upfront payment of $4 million and FTE research funding, and also expects to receive early technical milestones. Should the research result in compounds that enter clinical trials, Arena will receive clinical milestones along with royalties for an FDA approved and commercialized product. In addition to the upfront payment, Arena expects to receive over $10 million during the first year of this collaboration in research funding and milestone payments.

"Arena's broad access to human GPCRs using our proprietary micro-arrays has resulted in the identification of numerous exciting potential disease pathways and drug discovery targets. I am pleased that Merck has chosen to enter into this multi-year collaboration. Using Arena's screening technologies, we have quickly screened our chemical library, identified hits, and made significant progress in optimizing these hits into several chemical lead series. I expect that our Merck collaboration will allow us to more rapidly, and with greater confidence, expand upon and commercialize these discoveries," stated Jack Lief, President and Chief Executive Officer of Arena.

"Merck scientists are very enthusiastic about the opportunity to utilize Arena's cutting edge GPCR technology to further their drug discovery and development efforts," stated Dr. Bennett Shapiro, Executive Vice President Worldwide Licensing and External Research.

About Merck

Merck & Co., Inc. is a leading research-driven pharmaceutical products and services company. Merck discovers, develops, manufactures and markets a broad range of innovative products to improve human and animal health, directly and through its joint ventures.

About Arena

Arena's CART and Melanophore technologies allow for the direct identification of modulators of GPCRs in a ligand-independent manner, making the technologies particularly useful with respect to the many GPCRs of therapeutic interest in the

human genome. Arena has established collaborations with Eli Lilly and Company, Fujisawa Pharmaceutical Co., Ltd., Taisho Pharmaceutical Co., Ltd., TaiGen Biotechnology Co., and other companies. Arena has also initiated "Project Genesis," an internal program aimed at obtaining all of the human GPCRs, identifying the location of these receptors within the human body for purposes of understanding the function of such receptors, and screening each GPCR to identify receptor modulators that form the basis of drug candidates. For further information, please refer to Arena's website: http://www.arenapharm.com/ .

02/25/2004

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Arena Pharmaceuticals and **Merck**
G protein-coupled receptor (GPCR) therapeutics
Web Link: http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=ARNA&script=410&layout=-6&item_id=498841

Arena Pharmaceuticals Announces Achievement of $4 Million Success Milestone Under Merck Collaboration

SAN DIEGO, Feb 25, 2004 -- Arena Pharmaceuticals, Inc. (Nasdaq: ARNA) today announced the achievement of a $4 million milestone related to animal testing of small molecules that act upon selected G protein-coupled receptors (GPCRs), which may represent novel targets for cardiovascular disease. Arena and Merck have been collaborating since October 2002 on a group of GPCR targets discovered by Arena. Arena has performed high throughput small molecule screening on the target GPCRs, medicinal chemistry and subsequent in vitro and in vivo animal testing. The achieved preclinical milestone represents advancement in the potency and profile of identified small molecules in animal testing.

Dr. Dominic P. Behan, Arena's Vice President, Research, stated, "It's been a pleasure working with the sophisticated scientific team at Merck. This milestone marks an important breakthrough in our collaboration." Dr. Ismail Kola, Merck Senior Vice President, added, "We are very pleased that our collaboration with Arena has been successful in advancing identified small molecules in animal testing."

Arena is a biopharmaceutical company seeking to discover and develop drugs that act on an important class of drug targets called GPCRs. Arena initiated its first human studies on one of its internally discovered compounds for obesity in February 2004, which program is unrelated to the Merck collaboration. Arena uses its Constitutively Activated Receptor Technology, or CART(TM), Melanophore technology and other proprietary technologies to identify small molecules that may lead to new drugs in four major therapeutic areas: metabolic diseases, cardiovascular diseases, central nervous system disorders and inflammatory diseases.

Certain statements in this press release are forward-looking statements that involve a number of risks and uncertainties. Such forward-looking statements include statements about Arena's strategy, technologies, preclinical and clinical programs, future achievements, and statements that are not historical facts, including statements about Arena's ability to identify and develop small molecules or which are preceded by the words "will," "expect" or similar words. For such statements, Arena claims the protection of the Private Securities Litigation Reform Act of 1995. Actual events or results may differ materially from Arena's expectations. Important factors that could cause actual results to differ materially from those stated or implied by Arena's forward-looking statements are disclosed in Arena's SEC reports, including Arena's most recent quarterly report on Form 10-Q. These forward-looking statements represent Arena's judgment as of the date of this release. Arena disclaims any intent or obligation to update these forward-looking statements.

Arena Pharmaceuticals(R) and Arena(R) are registered service marks of the company. CART(TM) is an unregistered service mark of the company. Arena's headquarters are at 6166 Nancy Ridge Drive, San Diego, CA 92121, and its telephone number is (858) 453-7200. On the Internet, please refer to Arena's website: www.arenapharm.com for further information.

For further information, please contact: Jack Lief, President & CEO, ext. 223, or Dominic P. Behan, VP, Research, ext. 226, both of Arena Pharmaceuticals, Inc., +1-858-453-7200.

SOURCE Arena Pharmaceuticals, Inc.

Jack Lief, President & CEO, ext. 223, or Dominic P. Behan, VP, Research, ext. 226, both of Arena Pharmaceuticals, Inc., +1-858-453-7200

08/10/2004

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Arena Pharmaceuticals and **Merck**
G protein-coupled receptor (GPCR) therapeutics
Web Link: http://phx.corporate-ir.net/phoenix.zhtml?c=121703&p=irol-newsArticle&t=Regular&id=602638&

Arena Pharmaceuticals Announces Achievement of a $3 Million Milestone Under Merck Collaboration

SAN DIEGO, Aug 10, 2004 -- Arena Pharmaceuticals, Inc. (Nasdaq: ARNA) announced today the achievement of a $3 million milestone from Merck & Co., Inc. for assay development under their cardiovascular collaboration.

In October 2002, Arena and Merck entered into a collaboration focused on a group of GPCR targets discovered by Arena, which may represent novel targets for cardiovascular disease. Arena announced in the first quarter of 2004 the achievement of a $4 million milestone under this collaboration related to animal testing of small molecules in this program.

"We are pleased with Merck's commitment to the cardiovascular program and their further validation of our GPCR research programs," commented Dr. Dominic P. Behan, Arena's co-founder, Senior Vice President and Chief Scientific Officer. "We look forward to continuing our work with Merck to achieve our mutual goal of developing a successful product to treat cardiovascular disease."

About Arena Pharmaceuticals

Arena is a clinical stage biopharmaceutical company focusing on the discovery, development and commercialization of drugs in four major therapeutic areas: metabolic, cardiovascular, inflammatory and central nervous system diseases. Arena is developing a broad pipeline of compounds that act on an important class of drug targets called G protein-coupled receptors, or GPCRs, and that are being developed using Arena's proprietary technologies, including CART(TM) (Constitutively Activated Receptor Technology) and Melanophore. Arena also has research collaborations with Merck, Fujisawa, Taisho and TaiGen for products in a number of different indications. For additional information about Arena, visit their website at http://www.arenapharm.com/.

Forward-Looking Statements

Certain statements in this press release are forward-looking statements that involve a number of risks and uncertainties. Such forward-looking statements include statements about Arena's strategy, technologies, preclinical and clinical programs, ability to identify and develop drugs, future achievements, goals and expectations, as well as other statements that are not historical facts. For such statements, Arena claims the protection of the Private Securities Litigation Reform Act of 1995. Actual events or results may differ materially from Arena's expectations. Factors that could cause actual results to differ materially from the forward-looking statements include, but are not limited to, the timing, success and cost of Arena's research, out-licensing endeavors and clinical studies, Arena's ability to obtain additional financing, and the timing and receipt of payments and fees, if any, from Arena's collaborators. Additional factors that could cause actual results to differ materially from those stated or implied by Arena's forward-looking statements are disclosed in Arena's SEC reports, including Arena's most recent quarterly report on Form 10-Q. These forward-looking statements represent Arena's judgment as of the date of this release. Arena

disclaims any intent or obligation to update these forward-looking statements.

Arena Pharmaceuticals(R) and Arena(R) are registered service marks of the company. CART(TM) is an unregistered service mark of the company.

For further information, please contact: Jack Lief of Arena Pharmaceuticals, Inc., +1-858-453-7200, ext. 223
or Susan Neath of Atkins + Associates, +1-858-527-3486
for Arena Pharmaceuticals, Inc.

SOURCE Arena Pharmaceuticals, Inc.

http://www.arenapharm.com/

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R&D: Arena Pharmaceuticals
Client: Lilly

Date: 04/2000
Parties: Drug / Biotech
Type: Research, Collaboration, License
Subject: CART activation of GPCRs

Press Release(s):

$ Terms: Partial
Size ($M): $27.8
Equity ($M):
Royalty:

Disease: Cardiovascular, Central
Technology: Screening
Stage At Signing: Discovery